Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1342876

*Anatolian Curr Med J.* 2024;6(1):1-5

# Duodenal IgE and mast cells changes in diabetes mellitus patients

**Ethem Ömeroğlu, Ayşe Nur Uğur Kılınç**

Department of Medical Pathology, Konya Training and Research Hospital, Konya, Turkiye

**Cite this article as:** Ömeroğlu E, Uğur Kılınç AN. Duodenal IgE and mast cells changes in diabetes mellitus patients *Anatolian Curr Med J.* 2024;6(1):1-5.

**Received**: 14.08.2023 • **Accepted**: 10.11.2023 • **Published**: 15.01.2024

## ABSTRACT

**Aims**: To determine the differences in duodenal biopsies of diabetes mellitus (DM) patients and non-diabetic patients by investigating the numbers of immunoglobulin E (IgE) positive plasma cells, IgE positive mast cells, and eosinophils.

**Methods**: Patients diagnosed with chronic duodenitis and DM and those diagnosed only with chronic duodenitis within between 2010-2020 years were detected from the hospital information system. Paraffin blocks and hematoxylin-eosin-stained preparations of the patients' duodenal biopsies were obtained from the hospital's pathology archive. By performing IgE immunohistochemical staining for all blocks, the sections were evaluated through light microscopy.

**Results**: A total of 75 patients, 45 with DM and 30 non-diabetic patients with chronic duodenitis were included in the study. While IgE accumulation was prominently detected in the plasma cells and mast cells of DM patients' duodenal tissue samples, no significant IgE accumulation was detected in the biopsies of non-diabetic patients with chronic duodenitis.

**Conclusion**: To date, the effectiveness of mast cells, IgE, and duodenal histological changes in DM have been proven, but our study is the first to detect the increase in mast cells and IgE in duodenal biopsies of DM patients. High IgE in the duodenum could support the relationship between DM and food allergy. We consider that higher IgE antibodies detected in diabetic patients' duodenums will reveal promising novel results in elucidating DM pathophysiology and regulating the treatment modalities, and will shed light on future studies.

**Keywords**: Diabetes mellitus, Ig E, mast cells

## INTRODUCTION

The small intestine is a major organ involved in the digestion of food and absorption of nutrients and minerals. The duodenum, which is the first part of the small intestine and connects to the stomach, is a primary site in the digestion and absorption of food.[1]

Diabetes mellitus (DM), a chronic metabolic disease with hyperglycemia, is associated with abnormalities in structures and functions in the gastrointestinal tract, especially the small intestine.[2]

In the literature, duodenal biopsies in DM cases, it was found to be associated with decreased diameter of blood vessels, reduced number of endothelial fenestrae, microvasculature, edema, and mucosal ulcers in various studies.[3-5]

Finally, comprehensive histomorphology and quantitative analysis results explain decreased goblet cells, increased number of paneth cells, thickened submucosal layer, and enhanced duodenal glands in the diabetes mellitus group.[6]

In addition to these histologic studies, a study on the duodenal microenvironment in DM; patients with hyperglycemia had a higher duodenal bacterial count, increased pathobionts, and reduction in flora compared to normoglycemic.[7]

Mast cells are capable of powerful inflammatory response programs triggered by surface IgE cross-linking or through pattern recognition receptors. Human studies point to pathogenetic or protective mast cell functions in patients with atopic conditions, autoimmune disorders, type 2 diabetes, chronic urticaria, mastocytosis, and cancer.[8]

The type I hypersensitivity responses of classic allergic reactions are mediated by allergen cross-linking of immunoglobulin E (IgE) bound to FcεRI receptors on the surface of tissue mast cells. GI tissues are an important reservoir for allergen-specific IgE-positive plasma cells in allergic participants and could contribute significantly to allergen-specific serum IgE in the tissues and perhaps systemically.[9]

**Corresponding Author**: Ayşe Nur Uğur Kılınç, aysenurugur@hotmail.com

This work is licensed under a Creative Commons Attribution 4.0 International License.

In line with studies reporting that duodenal histopathological examination and mast cells are important in DM patients, in the present study, we aimed to determine the differences in duodenal biopsies of DM patients and non-diabetic patients by investigating the numbers of immunoglobulin E (IgE) positive plasma cells, IgE positive mast cells, and eosinophils.

## METHODS

The study was carried out with the permission of the KTO Karatay University Faculty of Medicine Non-drug and Medical Device Researches Ethics Committee (Date: 25.12.2020, Decision No: 2021.006). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The duodenum biopsy materials obtained from 45 diabetic patients and 30 non-diabetic individuals diagnosed with non-specific chronic duodenitis in the pathology laboratory of our hospital between 2010 and 2020 years were included and investigated in the study. The patients diagnosed with chronic duodenitis and DM and non-diabetic individuals diagnosed only with non-specific chronic duodenitis were detected from the hospital information system. The patients with any malignancy or diagnosed with any known food allergy and autoimmune disease were not included in the study. The paraffin blocks of patients' duodenal biopsy samples and hematoxylin-eosin-stained preparations were obtained from the hospital's pathology archive. In preparing tissue sections, poly-L-lysine (PPL) was used to coat glass slides for IgE immunocytochemical staining. The primary antibody was anti-human IgE (rabbit, Abcam, polyclonal, prediluted, Ab75673).

Therefore, immune-stained and hematoxylin-eosin-stained glasses were evaluated under a light microscope. With IgE staining, plasma cells with strong cytoplasmic staining were easily distinguishable from the mast cells with weaker membrane reactions. The numbers of Ig E-positive plasma cells and mast cells, eosinophils in the duodenal mucosa, and lamina propria were calculated by an ocular micrometer on a total area of mm² per sample. The IgE-containing mast cells were evaluated by counting cells in mm² in the areas where the cells were the most concentrated. However, the plasma cells containing IgE were graded as 1, 2, and 3 in light of their prevalence and density (**Figure 1-4**). The demographic data related to the patients' peripheral blood test results and ages were obtained from the hospital information system, and the data accessed were recorded.

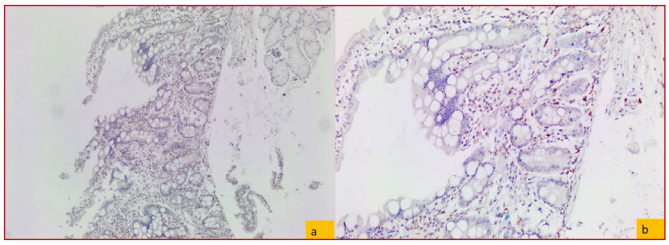


**Figure 1.** Diffuse and severe plasma cells containing IgE in the duodenum of the diabetic patient (IgE immunostaining image of 100X objective)(a), 200X objective(b)

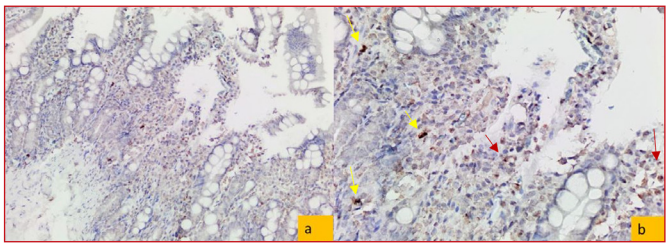


**Figure 2.** Focal and moderate Ig E containing plasma cells in the duodenum of the diabetic patient (Ig E immunostaining image of 100X objective)(a), 200X objective(b) (yellow arrows show some of the mast cells and red arrows show some of the plasma cells with IgE accumulation)

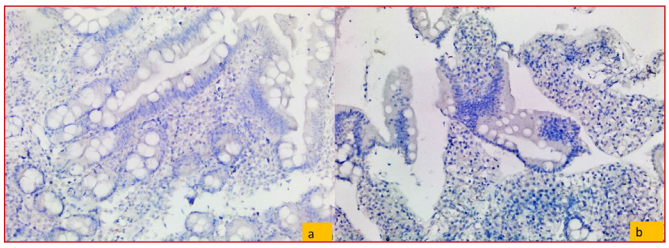


**Figure 3.** No plasma and mast cells accumulating Ig E in control group patient's duodenum 200X objective (a-b)

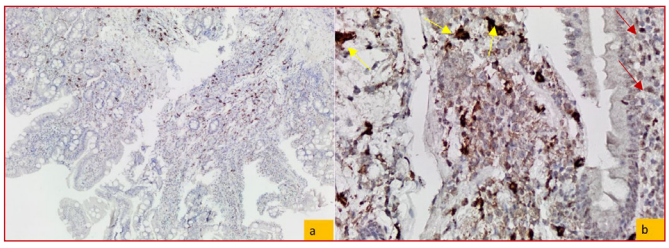


**Figure 4.** Severe mast cells containing Ig E in the duodenum of the diabetic patient, low magnification-100X(a), high magnification-400X(b), and moderate Ig E-containing plasma cells (yellow arrows show some of the mast cells and red arrows show some of the plasma cells with IgE accumulation).

While the differences between both groups were determined by the Mann-Whitney U test for numerical variables, the chi-square test was used to investigate the categorical variables. A p-value of <0.01 was considered statistically significant.

## RESULTS

Our study included a total of 75 patients, 45 with DM diagnosis [27 with type-1 DM and 18 with type-2 non-insulin-dependent DM (NIDDM)] and 30 non-diabetic patients diagnosed with chronic duodenitis. The study participants were classified as the study group consisting of 45 DM patients and the control group composed of 30

non-diabetic patients diagnosed with chronic duodenitis. DM and non-DM patients consist of groups with similar age distributions

While Ig E accumulation was detected in the plasma cells in duodenal tissue samples of DM patients, no significant Ig E accumulation was observed in duodenal tissue of non-diabetic patients (**Table**) (**Figure 1-3**). In addition to that, while the mast cells were seen in varying numbers in 77% (35/45) of DM patients, the cells were present only in 20% (6/30) of the participants in the control group (**Figure 4**).

**Table.** Demographic and histological results of Ig E staining, Mast cell, and plasma cells in duodenum biopsies of DM and non-DM patients

| | Diabetes mellitus patients | The control group (non-diabetes mellitus) patients | p-value |
|---|---|---|---|
| Mean Age/y | 40.8 | 38.1 | p>0.05 |
| The mean number of prevalence (diffusivity) of plasma cells containing IgE in duodenal biopsies | 1.6 | 0.06 | p<0.001 |
| The mean number of intensity of plasma cells containing IgE in duodenal biopsies | 1.9 | 0.06 | p<0.001 |
| Mast cells and plasma cells containing Ig E in duodenal biopsies/mm² | 17.7 | 0.6 | p<0.001 |

Based on our findings, both mast cells and IgE-containing plasma cells were found to be statistically significantly higher among DM patients, compared to those of the controls (p <0.01) (**Table** ).

Given the number of peripheral blood and tissue eosinophils, no significant difference was found between the study and control groups (p >0.05). Considering the plasma cells in type-1 and type-2 DM patients, no difference was detected between the number of IgE and mast cells and the number of tissue eosinophils (p >0.05).

## DISCUSSION

Increasing day by day and affecting individuals from all age segments across the world, DM is a chronic disease leading to fatal problems.[10] Numerous studies have been conducted to understand the pathophysiology of DM and are to be still performed.[11,12] In addition to these, medical science continues to create many medical and surgical novel treatment modalities to treat DM.[13-15]

There are many studies on the effectiveness of mast cells in DM patients.[8,16-18] Obesity is associated with adipose tissue inflammation and prominent M1 macrophage differentiation, as well as the dominance of type 1 cytokines, including TNF.[16] This spontaneous inflammatory response plays an important role in the breakdown of adipose tissue glucose homeostasis and the development of type II DM.[16] The observation that mast cells accumulate in the inflamed adipose tissue and reports on beneficial effects of H1- blocking and mast cell-stabilizing drugs with potentially additional anti-inflammatory effects on obesity and type II diabetes.[17,18]

In our study, the fact that a difference was determined between the two groups by examining the number of IgE-positive plasma cells, and the number of IgE-positive mast cells in DM and non-diabetic patients' duodenum biopsies yielded remarkable results never studied before.

In recent years, various studies have been conducted to demonstrate the associations between chronic inflammation, autoimmune diseases, and mast cells.[18,19] Even so, in diabetic individuals, it has been found that the severity of DM in plasma and tissue cells is associated with the number of mast cells.[20,21] As consistent with the findings stated by those studies, our study revealed that the rate of IgE-containing mast cells was higher in diabetic patients, compared to the control group.

As well as the above-mentioned ones, there are also studies detecting IgE in the plasma concentration of patients with DM. While some of those studies found that IgE was within normal limits, others revealed that the plasma IgE concentration was increased with the severity of DM.[20,24,25] Based on the literature, however, there is no study investigating IgE antibodies in the plasma cells and mast cells of the duodenal tissue of diabetic populations. So, our study findings are the first to enlighten the issue in this respect.

Given the findings related to IgE antibodies in the tissues, there are studies in the literature evaluating only food allergies in the duodenum and Helicobacter pylori in the stomach.[24-27] As a result of such studies, the detection of IgE in the duodenum tissue was found to be highly predictive and sensitive in detecting food allergies.[26]

We know from the literature that one of the components of diabetic gastroenteropathy is bacterial overgrowth and that bacterial overgrowth is generally associated with food intolerance and food allergy.[28,29] The IgE increase we detected in the duodenum may be associated with food allergy, which will cause bacterial overgrowth in DM patients. More detailed studies are needed on this subject.

There are some new studies asserting the relationship between DM and food allergy. These studies support that food allergen elimination reduces DM.[30,31] Our study detected more IgE in the duodenum of DM patients than in the control group and supported the food allergen and DM relationship which could help to reduce or reverse the progress of DM by food allergen elimination.[30,31]

Although blood eosinophil levels were found to be lower in the patients with insulin resistance and DM, compared to the control group in a study including a large population.[32] Other studies related to tissue eosinophils reveal the opposite. However, in studies evaluating the lipomatous tissues of the patients with metabolic syndrome and the pancreatic tissues of DM patients, the number of eosinophils and eosinophilic chemotactic proteins were demonstrated to be higher among the patients than in the control group.[32] In our study, no difference was found between blood eosinophil levels and tissue eosinophils in DM patients and the controls.

## CONCLUSION

To date, the effectiveness of mast cells, IgE, and duodenal histological changes in DM have been proven, but our study is the first to detect the increase of IgE in mast cells and plasma cells in duodenal biopsies of DM patients. High IgE in the duodenum supports the relationship between DM and food allergy. We consider that higher IgE antibodies detected in diabetic patients' duodenums will reveal promising novel results in elucidating DM pathophysiology and regulating the treatment modalities, and will shed light on future studies.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of the KTO Karatay University Faculty of Medicine Non-drug and Medical Device Researches Ethics Committee (Date: 25.12.2020, Decision No: 2021.006).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

## REFERENCES

1. Rao JN, Wang JY. Regulation of gastrointestinal mucosal growth. San Rafael (CA): Morgan & Claypool Life Sciences; 2010. Available from: https://www.ncbi.nlm.nih.gov/books/NBK54091/
2. Krishnan B, Babu S, Walker J, Walker AB, Pappachan JM. Gastrointestinal complications of diabetes mellitus. *World J Diabetes.* 2013;4(3):51-63.
3. Zhong HJ, Yuan Y, Xie WR, Chen MH, He XX. Type 2 diabetes mellitus is associated with more serious small intestinal mucosal injuries. *PLoS One.* 2016;11(9):e0162354.
4. Zhao M, Liao D, Zhao J. Diabetes-induced mechanophysiological changes in the small intestine and colon. *World J Diabetes.* 2017;8(6):249-269.
5. Kalaichelvi S. Prevalence of symptomatic peptic ulcer in diabetes mellitus patients at outpatient department of Government Medical College and Hospital in and around Villupuram District. *Int Arch Integrated Med.* 2018;5(2)111-115.
6. Darra A, Singh V, Jena A, et al. Hyperglycemia is associated with duodenal dysbiosis and altered duodenal microenvironment. *Scientific Rep.* 2023;13(1):11038.
7. Lerkdumnernkit N, Sricharoenvej S, Lanlua P, et al. The effects of early diabetes on duodenal alterations in the rats. *Int J Morphol.* 2022;40(2)389-395.
8. Maurer M, Taube C, Schröder NWJ, et al. Mast cells drive IgE-mediated disease but might be bystanders in many other inflammatory and neoplastic conditions. *J Allergy Clin Immunol.* 2019;144(4S):S19-S30.
9. Hoh RA, Joshi SA, Lee JY, et al. Origins and clonal convergence of gastrointestinal IgE+ B cells in human peanut allergy. *Sci Immunol.* 2020;5(45):eaay4209.
10. Sun P, Wen H, Liu X, Ma Y, Jang J, Yu C. Time trends in type 2 diabetes mellitus incidence across the BRICS from 1990 to 2019: an age-period-cohort analysis. *BMC Public Health.* 2022;22(1):65.
11. Lega IC, Lipscombe LL. Review: diabetes, obesity, and cancer-pathophysiology and clinical implications. *Endocr Rev.* 2020;41(1):bnz014.
12. Zaccardi F, Webb DR, Yates T, Davies MJ. Pathophysiology of type 1 and type 2 diabetes mellitus: a 90-year perspective. *Postgrad Med J.* 2016;92(1084):63-69.
13. Tan SY, Mei Wong JL, Sim YJ, et al. Type 1 and 2 diabetes mellitus: a review on current treatment approach and gene therapy as potential intervention. *Diabetes Metab Syndr.* 2019;13(1):364-372.
14. Brunkwall L, Orho-Melander M. The gut microbiome as a target for prevention and treatment of hyperglycaemia in type 2 diabetes: from current human evidence to future possibilities. *Diabetologia.* 2017;60(6):943-951.
15. Frydrych LM, Bian G, O'Lone DE, Ward PA, Delano MJ. Obesity and type 2 diabetes mellitus drive immune dysfunction, infection development, and sepsis mortality. *J Leukoc Biol.* 2018;104(3):525-534.
16. McNelis JC, Olefsky JM. Macrophages, immunity, and metabolic disease. *Immunity.* 2014;41(1):36-48.
17. Divoux A, Moutel S, Poitou C, et al. Mast cells in human adipose tissue: link with morbid obesity, inflammatory status, and diabetes. *J Clin Endocrinol Metab.* 2012;97(9):E1677-E1685.
18. Liu J, Divoux A, Sun J, et al. Genetic deficiency and pharmacological stabilization of mast cells reduce diet-induced obesity and diabetes in mice. *Nat Med.* 2009;15(8):940-945.
19. Wang Z, Zhang H, Shen XH, et al. Immunoglobulin E and mast cell proteases are potential risk factors of impaired fasting glucose and impaired glucose tolerance in humans. *Ann Med.* 2013;45(3):220-229.
20. Wang Z, Zhang H, Shen XH, et al. Immunoglobulin E and mast cell proteases are potential risk factors of impaired fasting glucose and impaired glucose tolerance in humans. *Ann Med.* 2013;45(3):220-229.
21. Divoux A, Moutel S, Poitou C, et al. Mast cells in human adipose tissue: link with morbid obesity, inflammatory status, and diabetes. *J Clin Endocrinol Metab.* 2012;97(9):E1677-E1685.

22. Liu J, Divoux A, Sun J, et al. Genetic deficiency and pharmacological stabilization of mast cells reduce diet-induced obesity and diabetes in mice. *Nat Med.* 2009;15(8):940-945.
23. Svensson J, Eising S, Mortensen HB, et al. High levels of immunoglobulin E and a continuous increase in immunoglobulin G and immunoglobulin M by age in children with newly diagnosed type 1 diabetes. *Hum Immunol.* 2012;73(1):17-25.
24. Maier LM, Howson JM, Walker N, et al. Association of IL13 with total IgE: evidence against an inverse association of atopy and diabetes. *J Allergy Clin Immunol.* 2006;117(6):1306-1313.
25. Caffarelli C, Romanini E, Caruana P, Street ME, de' Angelis G. Clinical food hypersensitivity: the relevance of duodenal immunoglobulin e-positive cells. *Pediatr Res.* 1998;44(4):485-490.
26. Andre F, Andre C, Descos L, Colin L, Cavagna S. Diagnosis of food allergy by counting IgE-positive duodenal cells. *Revue Française D'allergologie et D'immunologie Clinique.* 1993;33(2):119-123.
27. Berczi L, Sebestyén A, Fekete B, Tamássy K, Kopper L. IgE-containing cells in gastric mucosa with and without *Helicobacter pylori* infection. *Pathol Res Pract.* 2000;196(12):831-834.
28. Concepción Zavaleta MJ, Gonzáles Yovera JG, Moreno Marreros DM, et al. Diabetic gastroenteropathy: an underdiagnosed complication. *World J Diabetes.* 2021;12(6):794-809.
29. Zopf Y, Baenkler HW, Silbermann A, Hahn EG, Raithel M. The differential diagnosis of food intolerance. *Dtsch Arztebl Int.* 2009;106(21):359-370.
30. Willis FB, Susan P, Patch A. Prediabetes reduction from food allergen elimination. *Med Clin Case Rep.* 2023;3(1):1-3.
31. Willis FB, Shanmugam R, Sullivan JH, Rodriguez JP, Mouton CP. Food allergen elimination for obesity reduction; a longitudinal, case-control trial (n= 94): 2295. *Med Sci Sports Exercise.* 2022;54(9):671.
32. Hessner MJ, Wang X, Meyer L, et al. Involvement of eotaxin, eosinophils, and pancreatic predisposition in development of type 1 diabetes mellitus in the BioBreeding rat. *J Immunol.* 2004;173(11):6993-7002.